REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 1, 2, 3, 7 and 8 are amended herein to replace the terms "tolerable" and "customary" with the "pharmaceutically acceptable" and "pharmaceutically effective". Applicants submit that no new matter is presented by way of these amendments, as they clarify what was already claimed.

Priority document

In the outstanding Office Action, the Examiner notes that a copy of the certified copy of the priority document German Application No. 199 47 235.1, has not yet been provided. The certified copy of German Application No. 199 47 235.1 will follow shortly.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-2 and 7-8 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for the particular adrenoceptor agonists, salbuterol, reproterol, salmeterol, and formoterol, purportedly is not enabling for "any" adrenoceptor agonists employed in the pharmaceutical composition and the particular method of treatment for asthma or allergy recited in the claims herein. Applicants traverse.

As stated in *Ex parte Forman* (230 USPQ 546 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the

following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. A "patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. § 112, first paragraph. To this end, Applicants submit that the combination of what is set forth in the present specification with what is known renders the claims enabled by the specification.

The Office Action states that the present invention is highly unpredictable, because the skilled artisan purportedly could not identify or recognize members of the claimed genus by structure, formula or chemical name. Applicants submit this is not the case.

In order to be an effective agonist, the agonists have a common structure, especially with regard to binding site. A common structure of β2-adrenoreceptors is present, and it is this structure which imparts the common function. The binding site of these agonists at issue are the same, and must be in order to be effective agonists. To this end, Applicants submit that it is well know that there is a common mechanism for the action of β2-adrenoreceptor agonists. The whole group of β2-adrenoreceptor agonists is known to bind very specifically only to β2-adrenoreceptors which are expressed in bronchial and smooth muscle tissue. This biological activity is in contrast to the expression of β1-adrenoreceptors, which occurs mainly in cardiac tissue. (*see Drugs* 1971, Vol. 1, p. 274-302). β2-

adrenoreceptor agonists show very little or no affinity for β1-adrenoreceptors or α-adrenoreceptors. Binding of β2-adrenoreceptor agonists to the receptor may be competitively inhibited by β2-adrenoreceptor blockers (*see Drugs* 1991, Vol. 42(1), p. 115-137).

The mechanism of action is common for the group of β2-adrenoreceptor agonists, as their binding to the β2-adrenoreceptor results in the activation of adenylyl cyclase and stimulation of cAMP in the cell. cAMP is a well-known second messenger capable of triggering a sequence of cellular events that ultimately leads to the physiological effect. *See Drugs* 1989, Vol. 38(1), p. 77-122.

This bronchodilation effect is the same for all members of the group of β2-adrenoreceptor agonists. As noted in the Office Action, the specification is enabling for the specific agonists salbuterol, reproterol, salmeterol, and formoterol. As noted above, as the reaction cascade and primary binding sites of all agonists in this category are very specific, the skilled artisan would be able to combine what is known in the art with what is disclosed in the examples of the present specification to determine that that the claimed composition has a successful effect using the class of β2-adrenoreceptor agonists, and to determine appropriate β2-adrenoreceptor agonists.

The Office Action further argues that the skilled artisan would consider the present invention to be unpredictable with regard to therapeutic effects, side effects, and toxicity that may be generated by drug-drug interactions when administering the combination of any compounds represented by "adrenoceptor agonist" and loteprednol.

In light of the above, Applicants submit that the quantity of experimentation necessary is not undue and the amount of guidance and examples provided are sufficient, as the structure and functional properties of the four adrenoceptor agonists already noted as enabled, apply to all β2-adrenoreceptor agonists when used in the context of the claimed invention. Further, as shown above, the state of the art and skill in the art of β2-adrenoreceptors are such that the skilled artisan could practice the present invention, using what is provided in the specification.

In summary, as set forth in the Office Action, the specification is enabling for the specific agonists salbuterol, reproterol, salmeterol, and formoterol. Other adrenoceptor agonists would have similar therapeutic efficacy and properties, side effects, interactions with other drugs, and toxicity as they all share specific structural features. Thus, Applicants request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-8 stand rejected under 35 U.S.C. 112, second paragraph, as purportedly indefinite. The Office Actions states that the terms "tolerable" and "customary excipient" in the instant claims are purportedly not defined. Claims 1-3 and 7-8 are amended herein to replace "pharmaceutically tolerable ester" with "pharmaceutically acceptable ester" and "pharmaceutically effective ester". Applicants request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 1-8 stand rejected under 35 U.S.C. 103(a) as purportedly unpatentable over Doi, Bjermer and van der Molen.

Doi purportedly discloses that loteprednol etabonate is useful in a pharmaceutical composition because loteprednol etabonate has excellent anti-inflammatory and antiallergic activities. Bjermer purportedly discloses that long-acting agonists are bronchospasmolytics, and are used as inhalations in asthma treatment. van der Molen purportedly discloses that the symptoms of asthma patients are improved on inhalation of the long-acting agonists. The Office Action states that it would have been obvious to the skilled artisan to use loteprednol etabonate in connection with reproterol, salmeterol, or formoterol in a pharmaceutical composition, and a method for the treatment of allergies and/or airway disorders for simultaneous, sequential or separate administration. Applicants traverse.

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. 2142. Applicants respectfully submit that these criteria have not been met in the present Office Action.

The cited references as discussed below fail to recite all of the elements of the presently claimed invention and fail to provide an expectation of success or motivation to arrive at the claimed invention.

Doi

Doi discloses an aqueous suspension of loteprednol etabonate which may be useful in the treatment of inflammation and allergic disorders. However, the focus of Doi is the stable aqueous suspension of the active substance. To this end, the examples of Doi only concern stability of the suspension, and tolerability of the

suspension by the patients. There are no data provided regarding the efficacy of the substance in the treatment of any disorder, to support the efficacy of loteprednol etabonate as used in the present invention.

Thus, Doi fails to recite all of the elements of the claimed invention or provide motivation to the skilled artisan to modify Doi. Applicants submit it would not be obvious to the skilled artisan, learning from Doi that loteprednol alone may be effective in treating inflammation and allergy, that the same substance in combination with β2-adrenoreceptor agonists would result in the overadditive effect shown in present specification. Applicants refer the Examiner to Tables 1 and 2 (pages 5 and 6 respectively) as demonstrating this effect. In light of the above remarks, Applicants request that this rejection be withdrawn.

Bjermer and van der Molen

Both Bjermer and van der Molen disclose the supplementation of inhalative therapy of asthma bronchiale with "classical" corticosteroids by long-time β2-adrenoreceptor agonists. However, loteprednol is not a "classical" corticosteroid in the context of Bjermer and van der Molen, and thus does not apply to Bjermer and van der Molen.

Specifically, instead of being a "classical" steroid in the context of Bjermer and van der Molen, the loteprednol is a soft steroid. As noted on page 2 of the present specification, soft steroids have advantages over other steroids. For example, on page 2, lines 21-33, the specification recites that "[L]oteprednol belongs to the so-called soft corticosteroids. These two so-called soft corticosteroids (soft steroids) are distinguished in that they are activated by a so-called one-step reaction, i.e., by

hydrolases, esterases, without involvement of the mainly hepatically located cytochrome P450 monooxidase enzymes. Owing to this, only very low plasma concentrations occur, if at all, which are not sufficient to produce the classical corticosteroid side effects such as retardation of growth, osteoporosis or increase in the intraocular pressure".

Thus, not only do Bjermer and van der Molen fail to recite loteprednol, but the steroids they do recite do not have the same beneficial properties of loteprednol, as loteprednol does not cause the side effects associated with the steroids of the cited references. Applicants submit that the presently claimed invention is not obvious over Bjermer and van der Molen.

Finally, Applicants respectfully submit that unexpected results are in fact present with respect to the claimed methods. It is a well established legal precedent that the presence of an unexpected, advantageous or superior result is evidence of nonobviousness. *See* M.P.E.P. § 716.02(a); *In re Papesch*, 315 F.2d 381, 137 U.S.P.Q. 43 (C.C.P.A. 1963). Along these lines, it is also well established that "a greater than expected result" is evidence of nonobviousness. *See* M.P.E.P. § 716.02(a); *In re Corkill*, 711 F.2d 1496, 226 U.S.P.Q. 1005 (Fed. Cir. 1985).

As noted in the present specification, loteprednol in combination with β2-adrenoreceptor agonists results in an unexpected overadditive effect. In support, Applicants refer to Tables 1 and 2 of the present specification as demonstrating this effect. For example, Table 1 demonstrates the overadditive effect on the inhibition of TNF-alpha release upon combination of loteprednol and salbutamol, as opposed to these substances used individually.

In light of the above remarks, Applicants request that this rejection be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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